II. REMARKS

A. Status of the Claims

Claims 22 and 37 have been amended for proper antecedent basis.

It is respectfully submitted that no new matter has been added by virtue of the present amendments.

Claims 1-38 are pending.

B. Claim 38

In the Office Action mailed on January 31, 2011, claim 38 was objected to for being dependent on a rejected claim, and was not included in any of the outstanding rejections.

Claim 38 recites:

> The pharmaceutical composition of claim 1, wherein said naltrexone is naltrexone hydrochloride dihydrate.

The amendment filed on May 2, 2011, incorporated claim 38 into claim 1. In the telephonic interview of April 15, 2011, the Examiner confirmed that such an amendment will be entered. The amendment filed on May 2, 2011 should have overcome all of the rejections of record.

However, the Advisory Action mailed on May 23, 2011, indicated that the amendment filed on May 2, 2011 was not be entered, allegedly because the amendment made therein "is not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal," and despite the Examiner's indication that such an amendment will be entered.

At the same time, the Examiner expressly admitted on page 2 of the Advisory Action that "the prior art does not teach 'naltrexone hydrochloride dihydrate.'" The Examiner however stated "it is well within the skill of the art to include salt form of a known drug and absent a showing of secondary consideration as to why the hydrochloride dihydrate form is beneficial over any other salt form would be helpful in distinguishing the present invention." Id.

Applicants respectfully submit that it is not necessary to provide a showing of secondary consideration in the present case, because the Examiner has not establish the purported equivalency of naltrexone hydrochloride dihydrate and the naltrexone hydrochloride salts purportedly described in the cited references and has admitted on page 2 of the Advisory Action that "the prior art does not teach 'naltrexone hydrochloride dihydrate.'" In other words, the Examiner has not established a prima facie case of obviousness of claim 38.

Applicants respectfully submit that the combination of references cannot provide a reason for the skilled person to formulate a pharmaceutical composition comprising naltrexone hydrochloride dihydrate as recited in claim 38, because the combination of cited references does not mention naltrexone hydrochloride dihydrate.

An indication that claim 38 is allowable is earnestly solicited.

B. Claim Rejections- 35 U.S.C. § 103

1. U.S. 2003/0229111 to Oshlack et al. in view of U.S. Patent No. 5,866,164 Kuczynski et al.

Claims 1-14, 17-19, 22, 27-37 were rejected under 35 U.S.C. § 103(a) over U.S. 2003/0229111 to Oshlack et al. in view of U.S. Patent No. 5,866,164 to Kuczynski et al..

The rejection is respectfully traversed, for the reasons presented in the response filed on November 24, 2010, herein incorporated by reference, and for the reasons presented below.

Independent claims 1 and 22 each recites, in part, that the ratio of naltrexone to hydrocodone in the claimed compositions is from "0.011:1 to 0.0125:1."

Independent claim 27 recites, in part, that the ratio of naltrexone to hydrocodone in the claimed compositions is "0.0125:1."

The combination of the cited references does not describe the specific ratios recited in claims 1, 22 and 27. Further, there is nothing in the cited references that indicates that these ratios may be desirable or beneficial, or that the ratios of naltrexone to hydrocodone in the dosage forms of the cited references may need to be adjusted. The combination of the cited references therefore cannot provide a reason to the skilled person to alter the naltrexone to hydrocodone ratios exemplified in the Oshlack publication to the specific ratios recited in the present claims.

In response to the Examiner's statement on page 3 of the Office Action that "if naltrexone is in a dose of 0.056 mg and the hydrocodone is 5 mg, then the ratio is 0.011:1," Applicants respectfully submit that this statement is not based on the disclosure of the Oshlack publication, because there is no mention of a pharmaceutical composition comprising 0.056 mg of naltrexone and 5 mg of hydrocodone in the Oshlack publication. The Oshlack publication does not therefore provide a reason for the skilled person to pick these specific amounts out of great number of possibilities potentially encompassed by the generic disclosure of the Oshlack publication.

In response to the Examiner's statement on page 5 of the Office Action that "[i]t is obvious to vary and/or optimize the amount of hydrocodone and naltrexone provided in the composition, according to the guidance provided by Oshlack et al.," Applicants respectfully submit that, according to section 2144.05 of the Manual of Patent Examining Procedure:

> A particular parameter **must first** be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might

> be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio, and therefore the parameter optimized was not recognized in the art to be a result- effective variable.). See also *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) (prior art suggested proportional balancing to achieve desired results in the formation of an alloy).

The Board of Patent Appeals and Interferences also holds the view that it is not obvious to optimize the parameter which "was not recognized in the prior art as one that would affect the results." In re Whallen II, Appeal 2007-4423, July 23, 2008. "Obviousness cannot be proven merely by showing that a known composition could have been modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known composition in a way that would result in the claimed composition." Id.

As submitted in the previously filed responses, naltrexone to hydrocodone ratios in the hydrocodone/naltrexone compositions described in the Oshlack publication are significantly higher than the ratios recited in the present claims. For example, the naltrexone to hydrocodone ratio of Example 22 of the Oshlack publication is 0.025:1, which is double the highest naltrexone to hydrocodone ration recited in the present claims (i.e., 0.0125:1). The naltrexone to hydrocodone ratio of Example 20 of the Oshlack publication is 0.1:1, which is eight times higher than the 0.0125:1 ratio recited in the present claims.

Applicants submit that the combination of the cited references simply does not provide a reason to a skilled person to modify the naltrexone to hydrocodone ratios exemplified in the Oshlack publication by lowering the naltrexone to hydrocodone ratios disclosed in the Oshlack publication to the specific ratios recited in the present claims, because there is no suggestion in the cited references that the specific ratios recited in the present claims may be desirable or beneficial, or that the ratios of naltrexone to hydrocodone in the dosage form of the cited references may need to be adjusted.

With further regard to claims 2-11 and 30-34, Applicants respectfully submit that the combination of the cited references does not provide a reason for the skilled person to formulate a pharmaceutical composition comprising the exact amounts of naltrexone and hydrocodone recited in these claims. In fact, the Examiner has acknowledged on page 5 of the Office Action that the Oshlack publication "does not teach compositions with the exact amounts of naltrexone and hydrocodone as listed in claims 2-11 and 30-34 in one composition."

In response to the Examiner's statement on page 4 of the Office Action that "Table 20A exemplifies a composition comprising naltrexone hydrochloride in an amount of 0.5 mg and hydrocodone bitartrate in amount of 5 mg, meeting the limitation of claim 2," Applicants respectfully submit that the Examiner's assertion is incorrect. Claim 2 depends from claim 1 which recites naltrexone to hydrocodone ratio range of "0.011:1 to 0.0125:1." The ratio encompassed by the range recited in claim 2 is at least **ten times** lower than the naltrexone to hydrocodone ratio of Table 20A of the Oshlack publication (i.e., 0.1:1). Contrary to the Examiner's assertion, the limitation of claim 2 is therefore not met by Table 20A of the Oshlack publication.

In response to the Examiner's statement on page 4 of the Office Action that the disclosure of 5 mg of hydrocodone in Tables 22A, 23A, 24A, 25A, 26A, and 27A of the Oshlack publication "meet[s] the limitation of 'about' 7.5 mg hydrocodone" in present claim 3-5, Applicants respectfully submit that the skilled person would have realized that the term "**about** 7.5 mg of said hydrocodone" in present claim 3 does not encompass 5 mg hydrocodone, the amount which is about **37 %** lower than the value recited in present claim 3. Applicants respectfully note that present claim 2 already recites "about 5 mg ... hydrocodone." With respect to present claims 4 and 5, Applicants respectfully note that these claims recite "about 10 mg of ... hydrocodone" and "about 15 mg of ... hydrocodone," respectively, the amounts which also do not encompass the value of 5 mg recited in Tables 22A, 23A, 24A, 25A, 26A, and 27A of the Oshlack publication.

With further regard to claims 17 and 37, Applicants submit that the combination of the cited references does not provide a reason to the skilled person to formulate (i) a pharmaceutical composition, wherein hydrocodone and naltrexone are **substantially interdispersed** in a sustained release excipient as recited in claim 17, or (ii) an osmotic dosage form comprising **a drug layer comprising both** an opioid agonist and an opioid antagonist, because the Kuczynski patent describes dosage forms comprising opioid agonists and antagonists in **separate** layers.

In response to the Examiner's statements on page 5 and 7 of the Office Action that "Kuczynski et al. teaches osmotic dosage forms comprising hydrocodone and naltrexone in which hydrocodone and the opioid antagonist ... are included in one layer (see Examples 4 and 7)," Applicants submit that neither Example 4 nor Example 7 describes an osmotic dosage form in which hydrocodone and the opioid antagonist are included in one layer.

Example 7 of the Kuczynski recites:

> The dosage form further provided by the invention comprises a push displacement composition for pushing the hydromorphone composition from the dosage form, **consisting of** at least one of 15 to 500 mg of a poly(alkylene oxide) of 3,000,000 to 10,000,000 molecular weight, or 15 to 750 mg of an alkali carboxymethylcellulose, such as sodium carboxymethylcellulose, and potassium carboxymethylcellulose of 450,000 to 2,500,000 molecular weight; 0 to 500 mg and more preferred 5 to 350 mg of an osmagent, also known as osmotically effective solute, represented by magnesium sulfate, sodium chloride, sodium bicarbonate, sodium succinate, sodium succinate hexahydrate, lithium chloride, potassium sulfate, sodium sulfate, lithium sulfate, potassium acid phosphate, mannitol, urea, inositol, magnesium succinate, tartaric acid, carbohydrates such as raffinose, sucrose, glucose, lactose, fructose, sodium chloride and fructose, potassium chloride and dextrose; 0.01 to 20 mg of **an antagonist for an opioid**; 1 to 50 mg of a hydroxyalkylcellulose selected from the group consisting of hydroxyethylcellulose, hydroxypropylcellulose, hydroxyisopropylcellulose, hydroxybutylcellulose, hydroxypropylmethylcellulose, hydroxypropylethylcellulose, and hydroxypropylbutylcellulose, which hydroxyalkylcellulose comprises a 7,500 to 75,000 molecular weight; 0 to 10 mg of an antioxidant, represented by d-alpha tocopherol acetate, dl-alpha tocopherol, ascorbyl palmitate, ascorbic acid, butylated hydroxyanisole, butylated hydroxytoluene and propyl gallate; 0 to 10 mg of a lubricant, represented by magnesium stearate, calcium stearate, corn starch, potato starch,

bentonite, citrus pulp and stearic acid; and 0 to 10 mg of a colorant. (emphasis added).

Example 7 of the Kuczynski patent makes it clear that the push displacement composition described therein does not contain an opioid agonist, because Example 7 uses the term "consisting of" and does not mention opioid agonists when describing the composition of the push displacement layer.

Example 4 of the Kuczynski patent also does not teach or suggest an osmotic dosage form comprising a drug layer comprising both an opioid agonist and an opioid antagonist. Example 4 of the Kuczynski patent is directed to "[t]he antagonist composition according to the above examples [i.e., Examples 1-3], wherein the naloxone is replaced by a member selected from the group consisting of: naltrexone ...." See col. 4, l. 66, to col. 5, l. 4. Examples 1-3 describe dosage forms comprising bilayered cores coated with semipermeable membranes. See col. 2, l. 40, to col. 4, l. 64. The bilayered core comprises (i) a layer comprising an opioid agonist composition and (ii) a layer comprising an opioid antagonist composition. See, col. 2, l. 66, to col. 3, l. 3; and col. 4, ll. 1-6. Example 4 of the Kuczynski patent is therefore directed to dosage forms comprising opioid agonists and opioid antagonists in **separate** layers, rather than in one layer as recited in claim 37.

Accordingly, an osmotic composition formulated in accordance with the guidance provided by Examples 4 and 7 of the Kuczynski patent, would contain an opioid agonist and an opioid antagonist in separate layers, rather than in a single layer as recited in claim 38.

Reconsideration and withdrawal of the rejection is respectfully requested.

2. U.S. 2003/0191147 to Sherman et al. in view of U.S. 2003/0031712 to Kaiko et al. and U.S. Patent No. 5,866,164 to Kuczynski et al.

Claims 1-36 were rejected over the combination of U.S. 2003/0191147 to Sherman et al., U.S. 2003/0031712 to Kaiko et al. and U.S. Patent No. 5,866,164 to Kuczynski et al..

The rejection is respectfully traversed, for the reasons presented in the response filed on November 24, 2010, herein incorporated by reference, and for the reasons presented below.

Applicants respectfully submit that the combination of the cited references does not render the presently claimed naltrexone to hydrocodone ratios obvious, because the claimed ratios are not described in the cited references.

The Examiner states on page 6 of the Office Action that Example 15 of the Sherman publication "exemplifies the two compounds in a composition that falls within the claimed ratio."

Applicants respectfully disagree with the Examiner's assertion. Example 15 of the Sherman publication describes naltrexone to hydrocodone ratio of 0.01, which is at least 10% lower than the naltrexone to hydrocodone ratio recited in present claims 1 and 22 (i.e., 0.011:1); and is 25% lower than the ratio recited in present claim 27 (i.e., 0.0125:1). The ratio of Example 15 of the Sherman publication does not therefore meet the ratios of present claims 1, 22 and 27.

Further, there is nothing in the cited references that indicates that the specific ratios recites in claims 1, 22 and 27 may be desirable or beneficial, or that the ratios of naltrexone to hydrocodone in the dosage forms of the cited references may need to be adjusted. The combination of the cited references therefore cannot provide a reason to the skilled person to alter the naltrexone to hydrocodone ratios exemplified in the cited references to the specific ratios recited in the present claims.

The cited references do not provide a reason for the skilled person to pick the specific naltrexone to hydrocodone ratios recited in claims 1, 22 and 27 out of great number of possibilities potentially encompassed by the generic disclosure of the cited references.

Further, there is nothing in the cited references that suggests that the purported "optimization" of the dosage forms described in the cited references would result in the claimed naltrexone to hydrocodone ratios.

In response to the Examiner's statement on page 8 of the Office Action that "one of ordinary skill in the art at the time of the invention would have found it obvious to combine the teachings of Sherman et al. … and Kuczynski et al. which teaches osmotic dosage forms comprised of hydrocodone and naltrexone in one layer," Applicants respectfully note that, as explained above in response to the obviousness rejection over the combination of the Oshlack publication and the Kuczynski patent, the Kuczynski patent describes dosage forms comprising hydrocodone and naltrexone in separate layers, rather than in a single layer as asserted by the Examiner.

Reconsideration and withdrawal of the rejection is respectfully requested.

III. Conclusion

An allowance of the present application is earnestly solicited. According to currently recommended Patent Office policy, the Examiner is specifically authorized to contact the undersigned by telephone if the Examiner believes that a telephonic interview may advance the prosecution of the application.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Oleg Ioselevich, Reg. No. 56,963

DAVIDSON, DAVIDSON & KAPPEL, LLC
Patents, Trademarks and Copyrights
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940